Title: Genome-wide association study identifies 74 loci associated with educational attainment

Authors: All authors and their affiliations appear at the end of the paper

Summary: Educational attainment (EA) is strongly influenced by social and other environmental factors, but genetic factors are also estimated to account for at least 20% of the variation across individuals[1]. We report the results of a genome-wide association study (GWAS) for EA that extends our earlier discovery sample[1,2] of 101,069 individuals to 293,723 individuals, and a replication in an independent sample of 111,349 individuals from the UK Biobank. We now identify 74 genome-wide significant loci associated with number of years of schooling completed. Single-nucleotide polymorphisms (SNPs) associated with educational attainment are disproportionately found in genomic regions regulating gene expression in the fetal brain. Candidate genes are preferentially expressed in neural tissue, especially during the prenatal period, and enriched for biological pathways involved in neural development. Our findings demonstrate that, even for a behavioral phenotype that is mostly environmentally determined, a well-powered GWAS identifies replicable associated genetic variants that suggest biologically relevant pathways. Because EA is measured in large numbers of individuals, it will continue to be useful as a proxy phenotype in efforts to characterize the genetic influences of related phenotypes, including cognition and neuropsychiatric disease.

Main Text:

We study educational attainment (EA), which is measured in all main analyses as the number of years of schooling completed (*EduYears*, N = 293,723, mean = 14.33, SD = 3.61; Supplementary Information sections 1.1-1.2). All genome-wide association studies (GWAS) were performed at the cohort level in samples restricted to individuals of European descent whose EA was assessed at or above age 30. A uniform set of quality-control (QC) procedures

was applied to the cohort-level summary statistics. In our GWAS meta-analysis of ~9.3M SNPs from the 1000 Genomes Project, we used sample-size weighting and applied a single round of genomic control at the cohort level.

Our meta-analysis identified 74 approximately independent genome-wide significant loci. For each locus, we define the "lead SNP" as the SNP in the genomic region that has the smallest *P*-value (Supplementary Information section 1.6.1). Fig. 1 shows a Manhattan plot with the lead SNPs highlighted. The three SNPs that reached genome-wide significance in the discovery stage of our previous GWAS meta-analysis of EA[1] are also highlighted. The quantile-quantile (Q-Q) plot of the meta-analysis (Extended Data Fig. 1) exhibits inflation (λ_{GC} = 1.28), as expected under polygenicity[3].

Extended Data Fig. 2 shows the estimated effect sizes of the lead SNPs. The estimates range from 0.014 to 0.048 standard deviations per allele (2.7 to 9.0 weeks of schooling), with incremental R^2 in the range 0.01% to 0.035%.

To quantify the amount of population stratification in the GWAS estimates that remains even after the stringent controls used by the cohorts (Supplementary Information section 1.4), we used LD Score regression[4]. The regression results indicate that ~8% of the observed inflation in the mean χ^2 is due to bias rather than polygenic signal (Extended Data Fig. 3a), suggesting that stratification effects are small in magnitude. We also found evidence that the genetic association signals taken as a whole replicate reliably in several within-family analyses (Supplementary Information section 2 and Extended Data Fig. 3b).

To further test the robustness of our findings, we examined the within-sample and out-of-sample replicability of SNPs reaching genome-wide significance (Supplementary Information sections 1.7-1.8). We found that SNPs identified in the previous EA meta-analysis replicated in the new cohorts included here, and conversely, that SNPs reaching genome-wide

significance in the new cohorts replicated in the old cohorts. For the out-of-sample replication analyses of our 74 lead SNPs, we used the interim release of the U.K. Biobank [5] (UKB) (N = 111,349). As shown in Extended Data Fig. 4, 72 out of the 74 lead SNPs have a consistent sign ($P = 1.47\times10^{-19}$), 52 are significant at the 5% level ($P = 2.68\times10^{-50}$), and 7 reach genome-wide significance in the U.K. Biobank dataset ($P = 1.41\times10^{-42}$). For comparison, the corresponding expected numbers, assuming each SNP's true effect size is its estimated effect adjusted for the winner's curse, are 71.4, 40.3, and 0.6. (Supplementary Information section 1.8.2). We also find out-of-sample replicability of our overall GWAS results: the genetic correlation between *EduYears* in our meta-analysis sample and in the UKB data is 0.95 (s.e. = 0.021; Supplementary Table 1.14).

It is known that EA, cognitive performance, and many neuropsychiatric phenotypes are phenotypically correlated, and several studies of twins find that the phenotypic correlations partly reflect genetic overlap[6–8] (Supplementary Information section 3.3.4). Here, we investigate genetic correlation using our GWAS results for *EduYears* and published GWAS results for 14 other phenotypes, using bivariate Linkage-Disequilibrium (LD) Score regression[9]. First, we estimated genetic correlations with *EduYears*. As shown in Fig. 2, on average, alleles associated with greater EA are also associated with increased cognitive performance ($P = 9.9\times10^{-50}$) and intracranial volume ($P = 1.2\times10^{-6}$), increased risk of bipolar disorder ($P = 7\times10^{-13}$), decreased risk of Alzheimer's ($P = 4\times10^{-4}$), and lower neuroticism ($P = 2.8\times10^{-8}$). We also found positive, statistically significant, but very small, genetic correlations with height ($P = 5.2\times10^{-15}$) and risk of schizophrenia ($P = 3.2\times10^{-4}$).

Second, we examined whether our 74 lead SNPs are jointly associated with each phenotype (Extended Data Fig. 5 and Supplementary Information section 3.3.1). We reject the null hypothesis of no enrichment at $P < 0.05$ for 10 of the 14 phenotypes (all the exceptions are subcortical brain structures).

Third, for each phenotype, we tested (in the published GWAS results) each of our 74 lead SNPs or proxy for association at a significance threshold of 0.05/74. We found a total of 25 SNPs meeting this threshold for any of these phenotypes (but only one reaching genome-wide significance). While these results provide suggestive evidence that some of these SNPs may be associated with other phenotypes, further testing of these associations in independent cohorts is required (Supplementary Tables 3.2-3.4, Extended Data Fig. 6).

To consider potential biological pathways, we first tested whether SNPs in particular regions of the genome are implicated by our GWAS results. Unlike what has been found for other phenotypes, SNPs in regions that are DNase I hypersensitive in the fetal brain are more likely to be associated with *EduYears* by a factor of ~5 (95% confidence interval 2.89–7.07; Extended Data Fig. 7). Moreover, the 15% of SNPs residing in regions associated with histones marked in the central nervous system (CNS) explain 44% of the heritable variation (Extended Data Fig. 8a and Supplementary Table 4.4.2). This enrichment factor of ~3 for CNS ($P = 2.48\times10^{-16}$) is greater than that of any of the other nine tissue categories in this analysis.

Given that our findings disproportionately implicate SNPs in regions regulating brain-specific gene expression, we examined whether genes located near *EduYears*-associated SNPs show elevated expression in neural tissue. We tested this hypothesis using data on mRNA transcript levels in the 37 adult tissues assayed by the Genotype-Tissue Expression Project (GTEx)[10]. Remarkably, the 13 GTEx tissues that are components of the CNS—and only those 13 tissues—show significantly elevated expression levels of genes near *EduYears*-associated SNPs (FDR < 0.05; Extended Data Fig. 8b and Supplementary Table 4.5.2).

To investigate possible functions of the candidate genes from the GWAS associated loci, we examined the extent of their overlap with groups of genes ("gene sets") whose products are known or predicted to participate in a common biological process[11]. We found 283 gene sets significantly enriched by the candidate genes identified in our GWAS (FDR < 0.05;

Supplementary Table 4.5.1). To facilitate interpretation, we used a standard procedure[11] to group the 283 gene sets into "clusters" defined by degree of gene overlap. The resulting 34 clusters, shown in Fig. 3, paint a coherent picture, with many clusters corresponding to stages of neural development: the proliferation of neural progenitor cells and their specialization (the *cluster npBAF complex*), the migration of new neurons to the different layers of the cortex (*forebrain development*, *abnormal cerebral cortex morphology*), the projection of axons from neurons to their signaling targets (*axonogenesis*, *signaling by Robo receptor*), the sprouting of dendrites and their spines (*dendrite*, *dendritic spine organization*), and neuronal signaling and synaptic plasticity throughout the lifespan (*voltage-gated calcium channel complex*, *synapse part*, *synapse organization*).

Many of our results implicate candidate genes and biological pathways that are active during distinct stages of prenatal brain development. To directly examine how the expression levels of candidate genes identified in our GWAS vary over the course of development, we used gene expression data from the BrainSpan Developmental Transcriptome[12]. As shown in Extended Data Fig. 9, these candidate genes exhibit above-baseline expression in the brain throughout life but especially higher expression levels in the brain during prenatal development (1.36 times higher prenatally than postnatally, $P = 6.02\times10^{-8}$).

A summary overview of some promising candidate genes for follow-up work is provided in Table 1.

We constructed polygenic scores[13] to assess the joint predictive power afforded by the GWAS results (Supplementary Information section 5.2). Across our two holdout samples, the mean predictive power of a polygenic score constructed from all measured SNPs is 3.2% ($P = 1.18\times10^{-39}$; Supplementary Table 5.2 and Supplementary Information section 5).

Studies of genetic analyses of behavioral phenotypes have been prone to misinterpretation, such as characterizing identified associated variants as "genes for education." Such

characterization is not correct for many reasons: EA is primarily determined by environmental factors, the explanatory power of the individual SNPs is small, the candidate genes may not be causal, and the genetic associations with EA are mediated by multiple intermediate phenotypes[14]. To illustrate this last point, we studied mediation of the association between the all-SNPs polygenic score and *EduYears* in two of our cohorts. We found that cognitive performance can statistically account for 23-42% of the association ($P < 0.001$) and the personality trait "openness to experience" for approximately 7% ($P < 0.001$; Supplementary Information section 6).

It would also be a mistake to infer from our findings that the genetic effects operate independently of environmental factors. Indeed, a recent meta-analysis of twin studies found that genetic influences on EA are heterogeneous across countries and birth cohorts[15]. We conducted exploratory analyses in the Swedish Twin Registry to illustrate how environmental factors may amplify or dampen the impact of genetic influences (Supplementary Information section 7). We found that the predictive power of the all-SNPs polygenic score is heterogeneous by birth cohort, with smaller explanatory power in younger cohorts (Extended Data Fig. 10; see also Supplementary Information section 7.4 for discussion of the contrast between these results and findings from a seminal twin study that estimated EA heritability by birth cohort[16]).

Methods: All methods are described in the Supplementary Information.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Information Results can be downloaded from the SSGAC website (http://ssgac.org/Data.php). Data for our analyses come from many studies and organizations, some of which are subject to a MTA, and are listed in the Supplementary Information. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to D.J.B. (daniel.benjamin@gmail.com), D.C. (dac12@nyu.edu), P.D.K. (p.d.koellinger@vu.nl), or P.M.V. (peter.visscher@uq.edu.au).

Table 1 | Selected candidate genes implicated by bioinformatics analyses. Fifteen candidate genes implicated most consistently across various analyses. To assemble this list, each gene in a DEPICT-defined locus (Supplementary Information section 4.5) was assigned a score equal to the number of criteria it satisfies out of ten (see Supplementary Table 4.1 for details). The DEPICT prioritization *P*-value was used as the tiebreaker. "SNP": the SNP in the gene's locus with the lowest *P*-value in the *EduYears* meta-analysis. "Syndromic": which, if any, of three neuropsychiatric disorders have been linked to *de novo* mutations in the gene (Supplementary Information section 4.6). "Top-ranking gene sets": DEPICT reconstituted gene sets of which the gene is a top-20 member (Supplementary Table 4.5.1). The three most significant gene sets are shown if more than three are available. ID, intellectual disability; ASD, autism spectrum disorder; SCZ, schizophrenia.

Gene	SNP	Syndromic	Score	Top-ranking gene sets
TBR1	rs4500960	ID, ASD	6	Developmental biology, decreased brain size, abnormal cerebral cortex morphology
MEF2C	rs7277187	ID, ASD	5	ErbB signaling pathway, abnormal sternum ossification, regulation of muscle cell differentiation
ZSWIM6	rs61160187	–	5	Transcription factor binding, negative regulation of signal transduction, PI3K events in ErbB4 signaling
BCL11A	rs2457660	ASD	5	Dendritic spine organization, abnormal hippocampal mossy fiber morphology, SWI/SNF-type complex
CELSR3	rs11712056	SCZ	5	Dendrite morphogenesis, dendrite development, abnormal hippocampal mossy fiber morphology
MAPT	rs192818565	ID	5	Dendrite morphogenesis, abnormal hippocampal mossy fiber morphology, abnormal axon guidance
SBNO1	rs7306755	SCZ	5	Protein serine/threonine phosphatase complex
NBAS	rs12987662	–	5	–
NBEA	rs9544418	SCZ	4	Developmental biology, signaling by Robo receptor, dendritic shaft
SMARCA2	rs1871109	ID	4	–
MAP4	rs11712056	ASD	4	Developmental biology, signaling by Robo receptor, SWI-SNF-type complex
LINC00461	rs10061788	–	4	Decreased brain size, abnormal cerebral cortex morphology, abnormal hippocampal mossy fiber morphology
POU3F2	rs9320913	–	4	Dendrite morphogenesis, developmental biology, decreased brain size
RAD54L2	rs11712056	SCZ	4	Decreased brain size, SWI/SNF-type complex, nBAF complex
PLK2	rs2964197	–	4	Negative regulation of signal transduction, PI3K events in ErbB4 signaling

Authors:

Aysu Okbay[1,2,3,*], Jonathan P. Beauchamp[4,*], Mark A. Fontana[5,*], James J. Lee[6,*], Tune H. Pers[7,8,9,10,*], Cornelius A. Rietveld[1,2,3,*], Patrick Turley[4,*], Guo-Bo Chen[11], Valur Emilsson[12,13], S. Fleur W. Meddens[14,3,15], Sven Oskarsson[16], Joseph K. Pickrell[17], Kevin Thom[18], Pascal Timshel[19,8], Ronald de Vlaming[1,2,3], Abdel Abdellaoui[20], Tarunveer S. Ahluwalia[21,9,22], Jonas Bacelis[23], Clemens Baumbach[24,25], Gyda Bjornsdottir[95], Johannes H. Brandsma[26], Maria Pina Concas[27], Jaime Derringer[28], Nicholas A. Furlotte[29], Tessel E. Galesloot[30], Giorgia Girotto[31], Richa Gupta[32], Leanne M. Hall[33,34], Sarah E. Harris[35,36], Edith Hofer[37,38], Momoko Horikoshi[39,40], Jennifer E. Huffman[41], Kadri Kaasik[42], Ioanna P. Kalafati[43], Robert Karlsson[44], Augustine Kong[95], Jari Lahti[42,45], Sven J. van der Lee[2], Christiaan de Leeuw[14,46], Penelope A. Lind[47], Karl-Oskar Lindgren[16], Tian Liu[48], Massimo Mangino[49,50], Jonathan Marten[41], Evelin Mihailov[114], Michael B. Miller[6], Peter J. van der Most[51], Christopher Oldmeadow[52,53], Antony Payton[54,55], Natalia Pervjakova[56,114], Wouter J. Peyrot[57], Yong Qian[58], Olli Raitakari[59], Rico Rueedi[60,61], Erika Salvi[62], Börge Schmidt[63], Katharina E. Schraut[64], Jianxin Shi[65], Albert V. Smith[66,67], Raymond A. Poot[26], Beate St Pourcain[68,69], Alexander Teumer[70], Gudmar Thorleifsson[95], Niek Verweij[71], Dragana Vuckovic[31], Juergen Wellmann[72], Harm-Jan Westra[73,74,8], Jingyun Yang[75,76], Wei Zhao[77], Zhihong Zhu[11], Behrooz Z. Alizadeh[51,78], Najaf Amin[2], Andrew Bakshi[11], Sebastian E. Baumeister[70,79], Ginevra Biino[80], Klaus Bønnelykke[21], Patricia A. Boyle[75,81], Harry Campbell[64], Francesco P. Cappuccio[82], Gail Davies[35,83], Jan-Emmanuel De Neve[84], Panos Deloukas[85,86], Ilja Demuth[87,88], Jun Ding[58], Peter Eibich[89,90], Lewin Eisele[63], Niina Eklund[56], David M. Evans[68,184], Jessica D. Faul[91], Mary F. Feitosa[92], Andreas J. Forstner[93,94], Ilaria Gandin[31], Bjarni Gunnarsson[95], Bjarni V. Halldórsson[95,96], Tamara B. Harris[97], Andrew C. Heath[98], Lynne J. Hocking[99], Elizabeth G. Holliday[52,53], Georg Homuth[100], Michael A. Horan[101], Jouke-Jan Hottenga[20], Philip L. de Jager[102,103,8], Peter K. Joshi[64], Astanand

Jugessur[104], Marika A. Kaakinen[105], Mika Kähönen[106,107], Stavroula Kanoni[85], Liisa Keltigangas-Järvinen[42], Lambertus A.L.M. Kiemeney[30], Ivana Kolcic[108], Seppo Koskinen[56], Aldi T. Kraja[92], Martin Kroh[89], Zoltan Kutalik[109,60,61], Antti Latvala[32], Lenore J. Launer[110], Maël P. Lebreton[15,111], Douglas F. Levinson[112], Paul Lichtenstein[44], Peter Lichtner[118], David C.M. Liewald[35,83], LifeLines Cohort Study[113], Anu Loukola[32], Pamela A. Madden[98], Reedik Mägi[114], Tomi Mäki-Opas[56], Riccardo E. Marioni[35,115,11], Pedro Marques-Vidal[116], Gerardus A. Meddens[117], George McMahon[68], Christa Meisinger[25], Thomas Meitinger[118], Yusplitri Milaneschi[57], Lili Milani[114], Grant W. Montgomery[119], Ronny Myhre[104], Christopher P. Nelson[33,34], Dale R. Nyholt[120,119], William E.R. Ollier[54], Aarno Palotie[121,8,122,123,124,125], Lavinia Paternoster[68], Nancy L. Pedersen[44], Katja E. Petrovic[37], David J. Porteous[36], Katri Räikkönen[42,45], Susan M. Ring[68], Antonietta Robino[126], Olga Rostapshova[4,127], Igor Rudan[64], Aldo Rustichini[128], Veikko Salomaa[56], Alan R. Sanders[129,130], Antti-Pekka Sarin[124,131], Helena Schmidt[132,37], Rodney J. Scott[133,53], Blair H. Smith[134], Jennifer A. Smith[77], Jan A. Staessen[135,136], Elisabeth Steinhagen-Thiessen[87], Konstantin Strauch[137,138], Antonio Terracciano[139], Martin D. Tobin[140], Sheila Ulivi[126], Simona Vaccargiu[27], Lydia Quaye[49], Frank J.A. van Rooij[2,141], Cristina Venturini[49,50], Anna A.E. Vinkhuyzen[11], Uwe Völker[100], Henry Völzke[70], Judith M. Vonk[51], Diego Vozzi[126], Johannes Waage[21,22], Erin B. Ware[77,142], Gonneke Willemsen[20], John R. Attia[52,53], David A. Bennett[75,76], Klaus Berger[71], Lars Bertram[143,144], Hans Bisgaard[21], Dorret I. Boomsma[20], Ingrid B. Borecki[92], Ute Bültmann[145], Christopher F. Chabris[146], Francesco Cucca[147], Daniele Cusi[62,148], Ian J. Deary[35,83], George V. Dedoussis[43], Cornelia M. van Duijn[2], Johan G. Eriksson[149,45], Barbara Franke[150], Lude Franke[155], Paolo Gasparini[31,126,151], Pablo V. Gejman[129,130], Christian Gieger[24], Hans-Jörgen Grabe[152,153], Jacob Gratten[11], Patrick J.F. Groenen[154], Vilmundur Gudnason[12,67], Pim van der Harst[71,155,156], Caroline Hayward[41,157], David A. Hinds[29], Wolfgang Hoffmann[70], Elina Hyppönen[158,159,160], William G. Iacono[6], Bo Jacobsson[23,104], Marjo-Riitta Järvelin[161,162,163,164],

Karl-Heinz Jöckel[63], Jaakko Kaprio[32,124,56], Sharon L.R. Kardia[77], Terho Lehtimäki[165,166], Steven F. Lehrer[167,168], Patrik K.E. Magnusson[44], Nicholas G. Martin[169], Matt McGue[6], Andres Metspalu[114,170], Neil Pendleton[171,172], Brenda W.J.H. Penninx[57], Markus Perola[56,114], Nicola Pirastu[31], Mario Pirastu[27], Ozren Polasek[173,64], Danielle Posthuma[14,174], Christine Power[160], Michael A. Province[92], Nilesh J. Samani[33,34], David Schlessinger[58], Reinhold Schmidt[37], Thorkild I.A. Sørensen[175,9 ,68], Tim D. Spector[49], Kari Stefansson[95,67], Unnur Thorsteinsdottir[95,67], A. Roy Thurik[1,176,177,3], Nicholas J. Timpson[68], Henning Tiemeier[2,178,179], Joyce Y. Tung[29], André G. Uitterlinden[180,2], Veronique Vitart[41], Peter Vollenweider[116], David R. Weir[91], James F. Wilson[64,41], Alan F. Wright[41], Dalton C. Conley[181,182], Robert F. Krueger[6], George Davey Smith[68], Albert Hofman[2], David I. Laibson[4], Sarah E. Medland[47], Michelle N. Meyer[183], Jian Yang[11,184], Magnus Johannesson[185], Peter M. Visscher[11,184,#], Tõnu Esko[114,7,186,8,#], Philipp D. Koellinger[14,15,3,#], David Cesarini[18,187,#], Daniel J. Benjamin[188,5,#]

[*] These authors contributed equally.

[#] Designed and oversaw the study.

[1] Department of Applied Economics, Erasmus School of Economics, Erasmus University Rotterdam, 3062 PA, Rotterdam, The Netherlands

[2] Department of Epidemiology, Erasmus Medical Center, Rotterdam, 3015 GE, The Netherlands

[3] Erasmus University Rotterdam Institute for Behavior and Biology, Rotterdam 3062 PA, The Netherlands

[4] Department of Economics, Harvard University, Cambridge, MA 02138, USA

[5] Center for Economic and Social Research, University of Southern California, Los Angeles, CA 90089-3332, USA

[6] Department of Psychology, University of Minnesota Twin Cities, Minneapolis, MN 55455, USA

[7] Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA 2116, USA

[8] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA

[9] The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, University of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, 2100, Denmark

[10] Statens Serum Institut, Department of Epidemiology Research, Copenhagen, DK 2300, Denmark

[11] Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia

[12] Icelandic Heart Association, Kopavogur, 201, Iceland

[13] Faculty of Pharmaceutical Sciences, University of Iceland, 107 Reykjavík, Iceland

[14] Department of Complex Trait Genetics, VU University, Center for Neurogenomics and Cognitive Research, Amsterdam, 1081 HV, The Netherlands

[15] Amsterdam Business School, University of Amsterdam, Amsterdam, 1018 TV, The Netherlands

[16] Department of Government, Uppsala University, Uppsala, 751 20, Sweden

[17] New York Genome Center, New York, NY 10013, USA

[18] Department of Economics, New York University, New York, NY 10012, USA

[19] Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark Lyngby, 2800, Denmark

[20] Department of Biological Psychology, VU University Amsterdam, Amsterdam, 1081 BT, The Netherlands

[21] COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, 2820, Denmark

[22] Steno Diabetes Center, Gentofte, 2820, Denmark

[23] Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg, SE 416 85, Sweden

[24] Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, 85764, Germany

[25] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, 85764, Germany

[26] Department of Cell Biology, Erasmus Medical Center Rotterdam, 3015 CN, The Netherlands

[27] Istituto di Ricerca Genetica e Biomedica U.O.S. di Sassari, National Research Council of Italy, Sassari, 07100, Italy

[28] Psychology, University of Illinois, IL 61820, Champaign, USA

[29] 23andMe, Inc., Mountain View, CA 94041, USA

[30] Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, 6500 HB, The Netherlands

[31] Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, 34100, Italy

[32] Department of Public Health, University of Helsinki, Helsinki, FI-00014, Finland

[33] Department of Cardiovascular Sciences, University of Leicester, Leicester, LE3 9QP, UK

[34] NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK

[35] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, EH8 9JZ, UK

[36] Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[37] Department of Neurology, General Hospital and Medical University Graz, Graz, 8036, Austria

[38] Institute for Medical Informatics, Statistics and Documentation, General Hospital and Medical University Graz, Graz, 8036, Austria

[39] Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Oxford, OX3 7LE, UK

[40] Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK

[41] MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[42] Institute of Behavioural Sciences, University of Helsinki, Helsinki, FI-00014, Finland

[43] Nutrition and Dietetics, Health Science and Education, Harokopio University, Athens, 17671, Greece

[44] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, 171 77, Sweden

[45] Folkhälsan Research Centre, Helsingfors, FI-00014, Finland

[46] Institute for Computing and Information Sciences, Radboud University Nijmegen, Nijmegen, 6525 EC, The Netherlands

[47] Quantitative Genetics, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4029, Australia

[48] Lifespan Psychology, Max Planck Institute for Human Development, Berlin, 14195, Germany

[49] Department of Twin Research and Genetic Epidemiology, King's College London, London, SE1 7EH, UK

[50] NIHR Biomedical Research Centre, Guy's and St. Thomas' Foundation Trust, London, SE1 7EH, UK

[51] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, 9700 RB, The Netherlands

[52] Public Health Stream, Hunter Medical Research Institute, New Lambton, NSW 2305, Australia

[53] Faculty of Health and Medicine, University of Newcastle, Newcastle, NSW 2300, Australia

[54] Centre for Integrated Genomic Medical Research, Institute of Population Health, The University of Manchester, Manchester, M13 9PT, UK

[55] School of Psychological Sciences, The University of Manchester, Manchester, M13 9PL, UK

[56] Department of Health, THL-National Institute for Health and Welfare, Helsinki, FI-00271, Finland

[57] Psychiatry, VU University Medical Center & GGZ inGeest, Amsterdam, 1081 HL, The Netherlands

[58] Laboratory of Genetics, National Institute on Aging, Baltimore, MD 21224, USA

[59] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, 20521, Finland

[60] Department of Medical Genetics, University of Lausanne, Lausanne, 1005, Switzerland

[61] Swiss Institute of Bioinformatics, Lausanne, 1015, Switzerland

[62] Department Of Health Sciences, University of Milan, Milano, 20142, Italy

[63] Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, Essen, 45147, Germany

[64] Centre for Global Health Research, The Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, EH8 9AG, UK

[65] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892-9780, USA

[66] Icelandic Heart Association, Kopavogur, 201, Iceland

[67] Faculty of Medicine, University of Iceland, Reykjavik, 101, Iceland

[68] MRC Integrative Epidemiology Unit, University of Bristol, Bristol, BS8 2BN, UK

[69] School of Oral and Dental Sciences, University of Bristol, Bristol, BS1 2LY, UK

[70] Institute for Community Medicine, University Medicine Greifswald, Greifswald, 17475, Germany

[71] Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, 9700 RB, The Netherlands

[72] Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, 48149, Germany

[73] Divisions of Genetics and Rheumatology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, MA 02115, Boston, USA

[74] Partners Center for Personalized Genetic Medicine, Boston, MA 02115, USA

[75] Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL 60612, USA

[76] Department of Neurological Sciences, Rush University Medical Center, Chicago, IL 60612, USA

[77] Department of Epidemiology, University of Michigan, Ann Arbor, MI 48109, USA

[78] Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, 9713 GZ, The Netherlands

[79] Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, D-93053, Germany

[80] Institute of Molecular Genetics, National Research Council of Italy, Pavia, 27100, Italy

[81] Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL 60612, USA

[82] Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK

[83] Department of Psychology, University of Edinburgh, Edinburgh, EH8 9JZ, UK

[84] Saïd Business School, University of Oxford, Oxford, OX1 1HP, UK

[85] William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ, UK

[86] Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, 21589, Saudi Arabia

[87] The Berlin Aging Study II; Research Group on Geriatrics, Charité – Universitätsmedizin Berlin, Germany, Berlin, 13347, Germany

[88] Institute of Medical and Human Genetics, Charité-Universitätsmedizin, Berlin, Berlin, 13353, Germany

[89] German Socio- Economic Panel Study, DIW Berlin, Berlin, 10117, Germany

[90] Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK

[91] Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48109, USA

[92] Department of Genetics, Division of Statistical Genomics, Washington University School of Medicine, St. Louis, MO 63018, USA

[93] Institute of Human Genetics, University of Bonn, Bonn, 53127, Germany

[94] Department of Genomics, Life and Brain Center, University of Bonn, Bonn, 53127, Germany

[95] deCODE Genetics/Amgen Inc., Reykjavik, IS-101, Iceland

[96] Institute of Biomedical and Neural Engineering, School of Science and Engineering, Reykjavik University, Reykjavik 101, Iceland

[97] Laboratory of Epidemiology, Demography, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892-9205, United States

[98] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA

[99] Division of Applied Health Sciences, University of Aberdeen, Aberdeen, AB25 2ZD, UK

[100] Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, 17475, Germany

[101] Manchester Medical School, The University of Manchester, Manchester, 9PT, UK

[102] Program in Translational NeuroPsychiatric Genomics, Departments of Neurology & Psychiatry, Brigham and Women's Hospital, Boston, MA 02115, USA

[103] Harvard Medical School, Boston, MA 02115, USA

[104] Department of Genes and Environment, Norwegian Institute of Public Health, Oslo, N-0403, Norway

[105] Department of Genomics of Common Disease, Imperial College London, London, W12 0NN, UK

[106] Department of Clinical Physiology, Tampere University Hospital, Tampere, 33521, Finland

[107] Department of Clinical Physiology, University of Tampere, School of Medicine, Tampere, 33014, Finland

[108] Public Health, Medical School, University of Split, 21000 Split, Croatia

[109] Institute of Social and Preventive Medicine, Lausanne University Hospital (CHUV), Lausanne, 1010, Switzerland

[110] Neuroepidemiology Section, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892-9205, USA

[111] Amsterdam Brain and Cognition Center, University of Amsterdam, 1018 XA, Amsterdam, The Netherlands

[112] Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305-5797, USA

[113] LifeLines Cohort Study, University of Groningen, University Medical Center Groningen, Groningen, 9713 BZ, The Netherlands

[114] Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia

[115] Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[116] Department of Internal Medicine, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, 1011, Switzerland

[117] Tema BV, 2131 HE Hoofddorp, The Netherlands

[118] Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, 85764, Germany

[119] Molecular Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4029, Australia

[120] Institute of Health and Biomedical Innovation, Queensland Institute of Technology, Brisbane, QLD 4059, Australia

[121] Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA

[122] The Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA.

[123] Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114, USA

[124] Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, 00014, Finland

[125] Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA

[126] Medical Genetics, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, 34100, Italy

[127] Social Impact, Arlington, VA 22201, USA

[128] Department of Economics, University of Minnesota Twin Cities, Minneapolis, MN 55455, USA

[129] Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, IL 60201-3137, USA

[130] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL 60637, USA

[131] Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki 00300, Finland

[132] Research Unit for Genetic Epidemiology, Institute of Molecular Biology and Biochemistry, Center of Molecular Medicine, General Hospital and Medical University, Graz, Graz, 8010, Austria

[133] Information Based Medicine Stream, Hunter Medical Research Institute, New Lambton, NSW 2305, Australia

[134] Medical Research Institute, University of Dundee, Dundee, DD1 9SY, UK

[135] Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Science, University of Leuven, Leuven, 3000, Belgium

[136] R&D VitaK Group, Maastricht University, Maastricht, 6229 EV, The Netherlands

[137] Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, 85764, Germany

[138] Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig Maximilians-Universität, Munich, 81377, Germany

[139] Department of Geriatrics, Florida State University College of Medicine, Tallahassee, FL 32306, USA

[140] Department of Health Sciences and Genetics, University of Leicester, Leicester, LE1 7RH, UK

[141] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, 3015 GE, The Netherlands

[142] Research Center for Group Dynamics, Institute for Social Research, University of Michigan, Ann Arbor, MI 48104, USA

[143] Platform for Genome Analytics, Institutes of Neurogenetics & Integrative and Experimental Genomics, University of Lübeck, Lübeck, 23562, Germany

[144] Neuroepidemiology and Ageing Research Unit, School of Public Health, Faculty of Medicine, The Imperial College of Science, Technology and Medicine, London SW7 2AZ, UK

[145] Department of Health Sciences, Community & Occupational Medicine, University of Groningen, University Medical Center Groningen, Groningen, 9713 AV, The Netherlands

[146] Department of Psychology, Union College, Schenectady, NY 12308, USA

[147] Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari, 9042, Italy

[148] Institute of Biomedical Technologies, Italian National Research Council, Segrate (Milano), 20090, Italy

[149] Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, 00014, Finland

[150] Departments of Human Genetics and Psychiatry, Donders Centre for Neuroscience, Nijmegen, 6500 HB, The Netherlands

[151] Sidra, Experimental Genetics Division, Sidra, Doha 26999, Qatar

[152] Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, 17475, Germany

[153] Department of Psychiatry and Psychotherapy, HELIOS-Hospital Stralsund, Stralsund, 18437, Germany

[154] Econometric Institute, Erasmus School of Economics, Erasmus University Rotterdam, Rotterdam, 3062 PA, The Netherlands

[155] Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen. 9700 RB, The Netherlands

[156] Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, 1105 AZ, The Netherlands

[157] Generation Scotland, Centre for Genomics and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[158] Centre for Population Health Research, School of Health Sciences and Sansom Institute, University of South Australia, SA5000, Adelaide, Australia

[159] South Australian Health and Medical Research Institute, Adelaide, SA5000, Australia

[160] Population, Policy and Practice, UCL Institute of Child Health, London, WC1N 1EH, UK

[161] Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment & Health, School of Public Health, Imperial College London, London, W2 1PG, UK

[162] Center for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, FI-90014 , Finland

[163] Unit of Primary Care, Oulu University Hospital, Oulu, 90029 OYS, Finland

[164] Biocenter Oulu, University of Oulu, FI-90014 Oulu, Finland

[165] Fimlab Laboratories, Tampere, 33520, Finland

[166] Department of Clinical Chemistry, University of Tampere, School of Medicine, Tampere, 33014, Finland

[167] Economics, NYU Shanghai, 200122, Pudong, China

[168] Policy Studies, Queen's University, Kingston, K7L3N6, Canada

[169] Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4029, Australia

[170] Institute of Molecular and Cell Biology, University of Tartu, Tartu, 51010, Estonia

[171] Centre for Clinical and Cognitive Neuroscience, Institute Brain Behaviour and Mental Health, Salford Royal Hospital, Manchester, M6 8HD, UK

[172] Manchester Institute Collaborative Research in Ageing, University of Manchester, Manchester, M13 9PL, UK

[173] Faculty of Medicine, University of Split, Croatia, Split 21000, Croatia

[174] Department of Clinical Genetics, VU Medical Centre, Amsterdam, 1081 HV, The Netherlands

[175] Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, The Capital Region, Frederiksberg, 2000, Denmark

[176] Montpellier Business School, Montpellier, 34080, France

[177] Panteia, Zoetermeer, 2715 CA, The Netherlands

[178] Department of Psychiatry, Erasmus Medical Center, Rotterdam, 3015 GE, The Netherlands

[179] Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, 3015 GE, The Netherlands

[180] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, 3015 GE, The Netherlands

[181] Department of Sociology, New York University, New York, NY 10012, USA

[182] School of Medicine, New York University, NY 10016, New York, USA

[183] Bioethics Program, Union Graduate College - Icahn School of Medicine at Mount Sinai, Schenectady, NY 12308, USA

[184] The University of Queensland Diamantina Institute, The Translational Research Institute, Brisbane, QLD 4102, Australia

[185] Department of Economics, Stockholm School of Economics, Stockholm, 113 83, Sweden

[186] Department of Genetics, Harvard Medical School, Boston, MA 02115, USA

[187] Research Institute for Industrial Economics, Stockholm, 10215, Sweden

[188] Department of Economics, Cornell University, Ithaca, NY 14853, USA